Workshop Report

COVAX Clinical Development & Operations SWAT Team Workshop on *"COVID-19 vaccine development in an increasingly seropositive world"*

October 27th, 2021

Meeting report prepared by
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Executive summary

On 27th October 2021, the COVAX Clinical Development & Operations SWAT Team hosted a workshop on "COVID-19 vaccine development in an increasingly seropositive world." The main aim was to review the global epidemiology of past natural infection with SARS-CoV-2, provide an update on global vaccine delivery and uptake by vaccine type, review vaccine immune responses and efficacy among those with prior SARS-CoV-2 infection, and discuss current and future approaches to generate supportive efficacy data for vaccine licensure.

Key points included:

- The COVID-19 seropositivity rate is increasing worldwide and will likely continue to increase in both unvaccinated and vaccinated populations.
- Increasing seropositivity creates a challenging environment for public health decision-making and may also impact future vaccine development.
- Assay choice to determine baseline/pre-vaccination serostatus requires careful consideration.
- Vaccinating individuals previously infected with SARS-CoV-2 leads to very robust immune responses.
- Clover's COVID-19 vaccine is the first to demonstrate significantly reduced risk of COVID-19 disease in previously infected individuals.
- At least three times as many booster doses are administered daily as there are primary doses in low-income countries (LICs).
- COVAX is ramping up supply of COVID-19 vaccines, with four times the current supply expected by March 2022.
- Most heterologous booster trials have focused/are focusing on mRNA and viral vector platform vaccines. There is an urgent need to close corresponding gaps for vaccines used in low- and middle-income countries (LMICs).
- Data on the use of fractional doses of COVID-19 vaccines are urgently needed to potentially address vaccine supply shortages and for safety considerations – particularly in primed populations.
- CEPI has released a Call for Proposals (CfP) entitled "A platform trial approach to assess the immunogenicity and safety/reactogenicity of fractional COVID-19 vaccine(s) as an additional dose in primed populations (FraCT-CoV)." The CfP remains open to accept applications.
- A longitudinal analysis of mRNA vaccine-induced boosting responses demonstrated a diverse memory B cell pool at six months with many cells cross-reactive. The presence of a selection of memory cells facilitates heterologous boosting.
- Data from the ComCov study show that overall boosting with different vaccines (e.g., Moderna or Novavax) induces strong antibody responses, while priming with ChAdOx1 induces a strong CD4 response.
- The same beneficial impact (as that seen for influenza) on the supply of second generation COVID-19 vaccines can be expected if immuno-bridging for authorisation is adopted widely
- Cross platform bridging in clinical development is acceptable to a series of regulatory agencies for new COVID-19 vaccines, given the strong correlation/surrogacy of neutralising antibodies and vaccine-induced protection against COVID-19. Study designs should be based on non-inferiority if the comparator vaccine has high efficacy and superiority if the comparator vaccine has modest efficacy.
- Valneva's VLA2001 candidate vaccine demonstrated superiority against ChAdOx1 in terms of geometric mean titres (GMT) for neutralisation antibodies, as well as non-inferiority in terms of seroconversion rates at two weeks after the second vaccination in adults aged ≥30 years.
- One major challenge for the development of second-generation vaccines is to secure authorised comparator COVID-19 vaccines.

- It is essential to use the WHO international standard in a comparative immunogenicity trial.
- Immunogenicity studies can be conducted even when placebo-controlled clinical trials are still feasible.

The slideset from the meeting can be found here:
https://media.tghn.org/medialibrary/2021/10/20211027_Workshop_MASTER_DECK_FINAL.pdf

Agenda

Time (CET)	October 27, 2021 -Topics	Speaker(s)
15:00-15:10	**Part I - Welcome, meeting objectives and updates** • **Context setting for vaccine performance and evalations in setting of previously infected or vaccinated persons**	**Peter Dull, BMGF**
Part 1a. Vaccination among previously infected populations		
15:10-15:20	Global COVID-19 sero-prevalence studies – Current status, geographic patterns and temporal trends	**Emmanuelle Espie, CEPI**
15:20-15:30	Vaccination among the previously infected: Immunology and Effectiveness	**Florian Krammer, Icahn School of Medicine at Mount Sinai**
15:30-15:40	Vaccination among the previously infected – Lessons from Clover phase 3 efficacy study	**Htay Htay Han, Clover Pharmaceuticals**
Part 1b. Previously vaccinated populations		
15:40-15:50	Overview of COVID-19 vaccine delivery	**Emily Nickels, BMGF**
15:50-16:05	Updated results overview of homologous primary series and heterologous vaccinations and future look at research gaps	**Paul Oloo, CEPI** **Christof Vinnemeier, CEPI**
16:05-16:15	Heterologous vaccination: what can we anticipate in terms of breadth and durability?	**Robbert van der Most, CEPI**
16:15-16:25	Q&A for Part I	**Moderated by Peter Dull**
16:25-16:35	**Part II – Vaccine development approaches in setting of seropositivity: Are we ready to apply lessons learned from influenza?**	**Jakob Cramer, CEPI**
16:35-16:45	Lessons from past failures: How the USA Increased Its Access to Seasonal Influenza Vaccines 15 Years Ago	**Bruce Innis, PATH**
16:45-17:00	Correlation versus correlate: Considerations for immunologic comparative COVID-19 vaccine trials	**Edde Loeliger, CEPI**
17:00-17:10	Success criteria for phase 3 immunologic non-inferiority trial for COVID-19 vaccines	**Christian Taucher, Valneva**
17:10-17:55	Panel discussion: Regulatory considerations for approach to the demonstration of efficacy in setting of increased COVID-19 seropositivity ---- Relevance of learnings from influenza vaccines Panelists include:	

	• Adam Hacker, CEPI • Dean Smith, Health Canada • Rogerio Gaspar, WHO • Gustavo Santos, ANVISA • Phil Krause, FDA • In-sook Park, MFDS	
17:55-18:00	**Wrap Up & Next Steps**	**Jakob Cramer, CEPI**

Part I - Welcome, meeting objectives, and updates

Dr Peter Dull, Bill and Melinda Gates Foundation (BMGF), welcomed participants to the workshop. The aim of the workshop was to review the global epidemiology of past natural infection with SARS-CoV-2, provide an update on global vaccine delivery and uptake by vaccine type, review vaccine immune responses and efficacy among those with prior SARS-CoV-2 infection, and discuss current and future approaches to generate supportive efficacy data for vaccine licensure.

Dr Dull set the context for the workshop with the following key points:

- The COVID-19 vaccine development landscape at present includes 332 vaccine candidates of which 113 are in clinical trials and 22 in large-scale use.
- New challenges for COVID-19 vaccine development include:
    - Distribution remains unsatisfactory despite the availability of diverse vaccines with increasing volume.
    - Impressive performance is evident across several vaccine platforms; however, there are still questions regarding the durability of protection across different clinical endpoints, variable impact on variants, relatively high price, insufficient volume, deliverability (i.e., cold chain), and the continuing evolution of safety evaluations.
    - The environment for new vaccine development is shifting with placebo-controlled studies being more challenging but still ongoing (e.g., WHO Solidarity Trial), seropositivity increasing, and booster or "additional" dose becoming a new development target.
    - Each product may have different challenges; a high neutralising antibody titre might not be the primary driver of protection and National Regulatory Agencies (NRAs) are at different levels of acceptance with regards to immuno-bridging and non-inferiority.

Part 1a - Vaccination among previously infected populations

Global COVID-19 seroprevalence studies in unvaccinated populations, 2020-21

Dr Emmanuelle Espie, Coalition for Epidemic Preparedness Innovations (CEPI), provided an overview of the current status, geographical patterns, and temporal trends of global COVID-19 seroprevalence studies.

Key points included:

- The SARS-CoV-2 seropositivity rate is increasing worldwide; however, this increase varies by country and population.
- In high-income countries (HICs) where vaccination uptake is ≥60%, seropositivity in the remaining unvaccinated population is ~20% or less. In low- and middle-income countries (LMICs) where vaccination uptake remains low (<20% or even <5% in some African countries), seropositivity in the unvaccinated population can reach >50-60%.
- Variations in seroprevalence can result from differences in community transmission, population behaviour, and efficacy of public health response, but methodological limitations exist and should be considered in the interpretation of seroprevalence data. Studying a specific subpopulation (i.e., healthcare workers), selection of a small convenience sample, or utilising a test with imperfect sensitivity/specificity may for example overestimate seroprevalence.
- Recent estimates of seropositivity should be considered a minimum as seropositivity will likely continue to increase in both unvaccinated and vaccinated populations, given the disease dynamic and continuous circulation of the virus.

- Increasing seropositivity creates a challenging environment for public health decision-making. Vaccination recommendations to ensure the most appropriate and durable protection in those previously infected remain unclear.
- Increasing seropositivity may also impact future vaccine development as the potential control group progressively becomes smaller and more protected.
- Regular updates on seroprevalence to monitor immunity arising from both infection and vaccination, especially in LMICs, are essential.

Vaccination among the previously infected: Immunology and effectiveness

Dr Florian Krammer, Icahn School of Medicine at Mount Sinai, discussed the immunology and effectiveness of vaccination among individuals previously infected with SARS-CoV-2.

Summary points included:
- Infection induces long-lived anti-spike responses, even in individuals with mild (or asymptomatic) COVID-19.
- Assay sensitivity and/or persistence of immunity influences nucleoprotein (NP) seroprevalence. Thus, assay choice to determine serostatus requires careful consideration.
- Assay specificity might differ in low-income countries (LICs) as most assays have been developed in HICs and individuals in LICs might be exposed to different pathogens. It is therefore important to establish a baseline with pre-pandemic serum samples at the relevant location.
- Spike-binding IgG antibodies mounted upon natural infection provide significant protection from re-infection. It will be difficult to estimate vaccine efficacy compared to a previously infected control group.
- Studies conducted pre- and post-emergence of the Delta variant show that natural infection affords protection from reinfection (similar to mRNA vaccines).
- Numerous studies demonstrate that vaccinating individuals previously infected with SARS-CoV-2 leads to very robust immune responses.
- The following can be expected when vaccinating previously infected (or vaccinated) individuals:
    - A quick and robust anamnestic antibody response after one vaccination, which is also seen in sero-reverters. A second dose may not further increase the immune response.
    - Peak titres are often higher in pre-exposed than in naïve individuals even after one dose.
    - The timing between infection and vaccination may matter.
    - Not every vaccine may boost pre-existing immunity in the same way.
    - Boosting vaccine-induced pre-existing immunity may be different than boosting infection-induced pre-existing immunity.
    - Placebo-controlled trials with partially immune control groups would need to be very large.

Vaccination among the previously infected: Lessons from Clover's Phase 3 efficacy study

Dr Htay Htay Han, Clover Pharmaceuticals, presented lessons learned from SPECTRA, the Clover global Phase 2/3 trial.

Summary points included:
- SPECTRA successfully enrolled >30,000 adult and elderly participants in five countries across four continents.

- All SARS-CoV-2 strains observed in the efficacy analysis were variants, with Delta the predominant strain.
- Primary and secondary efficacy endpoints were successfully met, with 100% efficacy against severe COVID-19 and hospitalisation, 83.7% efficacy against moderate-to-severe COVID-19, and 67.2% efficacy against COVID-19 of any severity caused by any strain of SARS-CoV-2.
- Efficacy against COVID-19 of any severity caused by the globally dominant Delta strain was 78.7%.
- Clover's trimeric recombinant protein-based and adjuvanted COVID-19 vaccine had a favourable safety profile with no significant difference in systemic adverse events or severe/serious adverse events compared to placebo.
- This is the first COVID-19 vaccine to demonstrate significantly reduced risk of COVID-19 disease in previously infected individuals. The latter represents a growing and increasingly important population as SARS-CoV-2 continues to spread globally.

Part 1b - Vaccination among previously vaccinated populations

Overview of COVID-19 vaccine delivery

Dr Emily Nickels, BMGF, provided an overview of COVID-19 vaccine delivery.

Summary points included:
- Vaccine coverage varies by geography and income. In most African countries <10% of the population have received at least one dose of a COVID-19 vaccine.
- The cumulative percent of the population vaccinated in low, lower-middle, upper-middle, and high-income countries is 2%, 26%, 60%, and 66%, respectively.
- As of October 2021, 50 countries (70% HICs) started booster/additional dose administration.
- A booster program has been confirmed in six HICs (but have yet to start) and is being considered in at least 12 other countries.
- At least three times as many booster doses are administered daily as there are primary doses in LICs.
- Most countries have received ≥4 products. Thus, LICs, which usually have one product per disease, are being asked to manage multiple products to have available supply.
- Kenya was used as an example to highlight specific challenges countries are facing with regards to product influx. These include microplanning with limited supply visibility, managing different product profiles (i.e., cold chain requirements, immunisation schedules, training and administration, second dose follow up), prioritisation based on expiration, and availability of ancillary products (notably 0.3 ml syringes).
- COVAX is ramping up supply of COVID-19 vaccines, with four times the current supply expected by March 2022.

Heterologous COVID-19 booster vaccine studies and fractional doses

Dr Paul Oloo and Dr Christof Vinnemeier, CEPI, gave an overview of heterologous COVID-19 booster vaccine studies and fractional doses.

Key points included:
- mRNA vaccines are most reactogenic, particularly the Moderna vaccine (i.e., mRNA-1273).
- Use of Moderna, Janssen (Ad26.COV2.S), and Pfizer (BNT162b2) as booster vaccines leads to anamnestic serological responses after priming with Moderna, Pfizer, or Janssen vaccines.

- mRNA vaccines induce higher antibody titres in the first 28 days following boost compared to viral vectored vaccines.
- No safety concerns have thus far been identified.
- Most trials have focused/are focusing on mRNA and viral vector platform vaccines. There is an urgent need to close corresponding gaps for vaccines used in LMICs.
- Further data from heterologous boost studies are expected over the coming weeks and months. It will be important to assess which vaccines are preferential as a booster jab and the order of prime-boost administration, and to clarify the benefits of boosting for risk benefit assessment.
- Data on the use of fractional doses of COVID-19 vaccines are urgently needed to potentially address vaccine supply shortages and for safety considerations.
- The use of fractional doses has proven feasible with other vaccines (e.g., yellow fever, hepatitis B).
- Outstanding questions and challenges regarding the use of fractional doses include the target population (i.e., unprimed populations as primary immunisation, primed (special) populations, or individuals after natural infection), durability of antibody responses when boosted with fractional doses, selection of vaccine and dose, and practical challenges including securing vaccine supply for trials, administration of small volumes of vaccines, and syringe shortages.
- CEPI has released a Call for Proposals entitled "A platform trial approach to assess the immunogenicity and safety/reactogenicity of fractional COVID-19 vaccine(s) as an additional dose in primed populations (FraCT-CoV)" (https://cepi.net/wp-content/uploads/2021/10/FRACT-COV-CfP-text-05-Oct-2021.pdf). Technical and administrative questions should be directed to cfp@cepi.net.

Heterologous vaccination: what can we anticipate in terms of breadth and durability?

Dr Roberrt van der Most, CEPI, discussed breadth and durability of the immune response that might be anticipated following heterologous vaccination.

Key points included:
- Multiple variables require consideration in heterologous boosting, including different platforms, antigens, and time. Protection should be considered a function of antibody titre, durability, cell-mediated immunity (CMI), and innate immunity, while boostability should be considered a function of the number and specificities of memory B cells.
- A study of hepatitis B fractional dose boosting showed maintenance of memory B cell numbers; however, boosting was not heterologous.
- H5N1 influenza heterologous boosting (i.e., primed with Vietnam strain, boosted with Indonesia strain) showed different haemagglutinin-inhibiting antibody responses depending on the nature of immunological memory which could likely be explained by CD4 T helper cells. This indicates the importance of CMI and CMI analysis.
- An immunological framework for heterologous boosting using a B cell centric view was proposed. Primary vaccination induces B cell responses that depend on CD4 help for class switching, antibody affinity, and hypermutation. The latter helps generate B cell diversity and may enable the immune system to respond to different antigens and variants. B cells differentiate into memory B cells, which allow boosting, and plasma cells, which are responsible for the maintenance of titres.
- As a result of T cell help, memory B cells exist in different specificities (e.g., alpha-specific, beta-specific, delta-specific, cross-reactive). A boosting vaccine selects from this memory B cell pool; the quality of the cells in the memory B cell pool may determine how newly induced plasma cells drive novel titres.
- The aforementioned influenza study used an adjuvant to obtain Indonesia-specific antibodies from Vietnam-driven memory cells.
- A longitudinal analysis of mRNA vaccine-induced boosting responses demonstrated a diverse memory B cell pool at six months with many cells cross-reactive. The presence of a selection of memory cells facilitates heterologous boosting.

- Data from the ComCov study show that overall boosting with different vaccines (e.g., Moderna or Novavax) induces strong antibody responses, while priming with ChAdOx1 induces a strong CD4 response.

Q&A session

A Q&A session included the following key points:

- *Do data support a specific platform (rather than specific product) as a preferential additional dose (as part of a heterologous mixed primary schedule)?*
    - Priming with adenoviral vector is efficient for generating T cell responses that are boostable; results from ComCov suggest this platform performs somewhat better than mRNA.
    - Different combinations work well in terms of antibody boostability. Boosting with adjuvanted protein appears comparable to mRNA vaccines. The least efficient combination is likely adeno-adeno.
    - The B cell pool generated by different platforms is capable of generating cross reactive responses to different SARS-CoV-2 variants.

- *Might a different dynamic be evident (than that seen with the heterologous primary series) if an additional dose is administered at a six-month time point?*
    - ChAdOx1 data have shown that antibodies against the vector itself decrease over time while the memory B cell pool matures.
    - This expansion and evolution of the memory B cell pool may increase the capacity to boost and respond to different variants over time.

- *What might the efficacy of the Clover vaccine be on the background of a prior exposure to Beta, Delta, or a different variant?*
    - At present, specific information regarding prior strains is not available. However, it is known that the original Wuhan strain was the predominant circulating strain in 2020. Thus, most individuals were likely exposed to this strain. From early 2021, different variants (i.e., Alpha, Delta) have been in circulation. Clover is currently considering what exploratory analysis or testing to conduct to assess any differences in vaccine efficacy depending on prior strain exposure.

- *How important is a variant boost considering discussions around original antigenic sin?*
    - Original antigenic sin is likely not a concern at present as SARS-CoV-2 variants are not so far escaped that they use different or competing memory B cell pools.
    - A problem could arise if divergence between strains evolves in a similar way to influenza (i.e., just sufficiently different to not use the same B cells). However, the addition of an adjuvant (i.e., CD4 cell response) solved this issue in the aforementioned influenza study. The fact that most available COVID-19 vaccines induce appropriate CMI responses ensures a good breadth of response.
    - How the pandemic will evolve, which new strains arise, and to what extent these strains stretch the patience of the current B cell pool will become clearer over time. In the meantime however, product developers should continue to engage in these conversations.

Part II - Vaccine development approaches in setting of seropositivity: Are we ready to apply lessons learned from influenza?

Lessons from past failures: How the USA increased its access to seasonal influenza vaccines 15 years ago

Dr Bruce Innis, PATH, discussed lessons learned from influenza relevant to the current challenge of increasing access to next-generation COVID-19 vaccines.

Summary points included:

- In October 2004 the US Food and Drug Administration (FDA) blocked import of all 48 million doses of Chiron's influenza vaccine from its Liverpool facility resulting in a severe vaccine shortage for the US influenza immunisation campaign.
- Numerous sponsors (n=6) used the immuno-bridging pathway to license new influenza vaccines.
- Post-marketing vaccine efficacy studies confirmed clinical benefit in preventing influenza.
- The US, which has a recommendation to vaccinate all persons aged six months or older, is today able to immunise >180 million people a year.
- The same beneficial impact on the supply of second generation COVID-19 vaccines can be expected if immuno-bridging for authorisation is adopted widely.
- Evidence supporting the haemagglutination-inhibition (HI) surrogate endpoint (for influenza) was no more robust than the current evidence supporting the correlation of SARS-CoV-2 spike antibody with vaccine efficacy in trials of diverse COVID-19 vaccines that elicit immunity to S protein.
- Intra-pandemic effectiveness may be confirmed in observational studies (e.g., test-negative case-control design).

Surrogate markers and correlates of protection: immuno-bridging in an increasingly primed population

Dr Edde Loeliger, CEPI, discussed the development of new COVID-19 vaccines based on immuno-bridging (not including development of strain-adapted vaccine).

Key points included:

- A surrogate endpoint/marker represents a measure of the effects of a specific treatment that may correlate with a real clinical endpoint but does not necessarily have a guaranteed relationship. Numerous generic and new drug approvals, as well as label extensions, are based on non-inferiority of an accepted surrogate.
- Label extensions for prophylactic vaccines often use bridging trials (based on a surrogate) to extend the efficacy to age groups or other groups not included in the original trial. This also happens for vaccines for which there is no correlate of protection.
- There are numerous examples of within platform immuno-bridging on antibody surrogate endpoints in the absence of a strong correlate of protection (e.g., dengue vaccines).
- The non-inferiority trial is the most common bridging trial. It seeks to determine whether a new intervention is no worse than a reference intervention. A pre-stated margin of non-inferiority for the treatment effect is defined and represents the smallest value that would be a clinically important effect; this can be directly measured as a clinical outcome, or indirectly using a surrogate marker.
- Both seasonal influenza vaccines and COVID-19 vaccines have immune markers that are reasonably likely to predict the clinical benefit of vaccines. The influenza surrogate marker is anti-haemagglutinin (anti-HA; HI) titres, whereas the COVID-19 surrogate marker is virus neutralising antibodies and IgG binding antibodies. For both, protection from illness is increased for vaccines with higher antibody titres.

- There is no correlate of protection for COVID-19, whereas for influenza a four-fold increase in anti-HA titres provides 50% protection against illness.
- The FDA's accelerated approval pathway for new seasonal influenza vaccines includes cross platform bridging.
- Cross platform bridging in clinical development is acceptable to a series of regulatory agencies for new COVID-19 vaccines, given the strong correlation/surrogacy of neutralising antibodies and vaccine-induced protection against COVID-19. A statement from the Access Consortium says that immunogenicity bridging studies can be used if clinical endpoint efficacy studies are no longer feasible, and neutralising antibody titre may be used in immunogenicity bridging studies as immune marker to predict vaccine effectiveness for new vaccines. Study designs should be based on non-inferiority if the comparator vaccine has high efficacy and superiority if the comparator vaccine has modest efficacy.
- Considerations for COVID-19 cross platform bridging include:
    - The inclusion of seroconversion (in naïves) or seroresponse rates (in primed population) as endpoints is not a measure of clinical benefit but to ensure non-inferior distribution of GMTs.
    - Studies conducted by Valneva and SK Biosciences are recent examples of COVID-19 cross platform bridging.

Success criteria for Phase 3 immunological non-inferiority trial for COVID-19 vaccines

Dr Christian Taucher, Valneva, presented results from the VLA2001 Cov-Compare study.

Key points included:
- The trial met its co-primary endpoints. VLA2001 demonstrated superiority against ChAdOx1 in terms of GMT for neutralisation antibodies, as well as non-inferiority in terms of seroconversion rates at two weeks after the second vaccination (i.e., Day 43) in adults aged ≥30 years.
- VLA2001 was generally well tolerated.
    - The tolerability profile of VLA2001 was significantly more favourable compared to the active comparator vaccine.
    - Participants aged ≥30 years reported significantly fewer solicited adverse events up to seven days after vaccination, both with regards to injection site and systemic reactions.
    - Participants in the younger age group vaccinated with VLA2001 showed an overall safety profile comparable to the older age group.
- The occurrence of COVID-19 cases (exploratory endpoint) was similar between treatment groups in participants aged ≥30 years.
- The complete absence of any severe COVID-19 cases may suggest that both vaccines used in the study prevented severe COVID-19 caused by the circulating variant(s) (predominantly Delta).
- T-cell responses analysed in a subset of participants showed that VLA2001 induced broad antigen-specific interferon-gamma producing T cells reactive against the S, N and M proteins.

Panel discussion

A panel discussion on regulatory considerations for the demonstration of efficacy in the setting of increased COVID-19 seropositivity included the following key points:

- *In-Sook Park, MFDS, South Korea –*

- Immuno-bridging studies comparing neutralising antibodies between the candidate and an approved vaccine are currently accepted in South Korea due to the high vaccination rate. The decision to allow this is based on evidence showing strong correlation between efficacy and neutralising antibody.
- A Phase 3 trial of SK Bioscience's protein-based vaccine has recently been approved in South Korea. The trial will be a randomised, blinded, superiority study to compare immunogenicity of the candidate vaccine with ChAdOx1 in terms of GMT ratio for neutralising antibody titre. In addition, T cell immunity is expected to play a role in long-term immunogenicity, higher effectiveness against variant viruses, and alleviation in disease severity.
- One major challenge for the development of second-generation vaccines is to secure authorised comparator COVID-19 vaccines.
- It is essential to use the WHO international standard and a fully validated analytical method in a comparative immunogenicity trial.

- *Phil Krause, US FDA* -
  - Immunogenicity studies can be conducted even when placebo-controlled clinical trials are still feasible. Further COVID-19 vaccines are required, and efficacious vaccines can be made available more rapidly without conducting placebo-controlled trials.
  - Candidate vaccines that elicit an immune response equivalent to that of the most efficacious vaccines merit an early approval pathway (i.e., deployment and evaluate efficacy in a post-deployment setting). The International Coalition of Medicines Regulatory Authorities (ICMRA) has suggested that immunogenicity can be non-inferior if the comparator vaccine has high efficacy or superior if the comparator has moderate efficacy. Exact cut-offs however have not been agreed.
  - COVID-19 is still an international public health emergency and thus the regulatory mechanisms that exist (as opposed to routine licensure setting) should be considered in determining how matters are conducted.
  - Post-authorisation studies are increasingly challenging due to the decreasing availability of a control group. Randomised deployment (i.e., timing of intervention is used to generate the control groups) can be considered an alternative. This could also be used to study fractional dosing or lower versus higher dosing in a deployment setting rather than a clinical trial setting.
  - Available serological assays may not always correctly identify seronegative individuals. Thus, simply comparing vaccines against a specific standardised level might not be sufficient. Rather, if a level can be identified that the most efficacious vaccines meet which is based on the international standard, candidate vaccines that meet that level might be able to be deployed more rapidly if adequate safety data was available.

- *Gustavo Santos, ANVISA* -
  - The current situation in Brazil is challenging as >90% of the population have been vaccinated with at least one dose making placebo-controlled trials difficult to conduct, new vaccines and technologies are being proposed internationally, and there are some local initiatives for vaccines with different platforms and different technologies.
  - The Brazilian regulatory agency (ANVISA) agrees with the ICMRA consensus and is advising developers to conduct immuno-bridging studies to achieve minimum regulatory requirements for approval. Comparison of both neutralising and binding antibodies are requested.

- Such trials in Brazil are still preclinical or just about to enter Phase 1, with no results yet available. It is understood that if clinical endpoints and follow up are included as a regulatory requirement for such studies, timely results will not be available.
- Commitments that developers have agreed with regulators are an important part of regulatory approval. The continuous and growing knowledge that may be gained from commitments (i.e., follow up, efficacy, safety) is of important value.

- *Rogerio Gaspar, World Health Organisation (WHO) -*
  - WHO's priority is to attain 40% vaccine coverage in each country by the end of 2021.
  - It is likely that an influenza-like approach with regards to vaccine development may be required from the regulators following the pandemic phase of COVID-19. However, moving directly to an influenza-like scenario is still too soon.
  - With regards to immunogenicity studies, issues include serology (especially assays and controls) and the failure to use WHO reference standards.
  - Despite numerous barriers and methodological issues, vaccine effectiveness studies are required to monitor the evolution of vaccine efficacy against target populations.
  - Whether the licensure pathway for future COVID-19 vaccines will follow that of influenza should be data driven. The quality of data will be essential, as will an open collaboration between regulators, research, and manufacturers. WHO is focused on identifying the evolution of variants of concern as part of that process and has recently established a framework with two external expert panels, one on the variants of evolution and another that will provide information for changes in vaccine composition.
  - The pandemic has resulted in a global collaboration between regulators, manufacturers, relevant stakeholders, and the scientific community which should continue into the future when some of these critical decisions might need to be made.

- *Dean Smith, Health Canada -*
  - The Access Consortium recognises that neutralising antibody is an important, but not the only, marker. The utility of animal models, challenge studies, and characterisation of induced responses relevant to variants of concern can be used to support an authorisation.
  - Access Consortium members agree that well-justified and appropriately designed immuno-bridging studies are an acceptable approach for authorising COVID-19 vaccines. The Consortium provides additional considerations for cross-platform immuno-bridging.
  - Certain vaccine types, for example peptide vaccines, may not be appropriate for an immuno-bridging study as they may not induce high neutralising antibody titres yet still be effective. The latter could only potentially be demonstrated through a placebo-controlled trial or other mechanism.
  - Compared to immuno-bridging, randomised designs are as robust but potentially quicker and could avoid the challenges of accessing relevant comparators. Health Canada is open to any rationally designed, data-supported approach to an authorisation pathway.
  - Agencies will make risk benefit decisions regarding emergency authorisations relevant to its own population in a data driven way and those decisions should be respected.

- *Adam Hacker, Head of Global Regulatory Affairs, CEPI -*
    - Regulators initially emphasised the importance of comparing candidate vaccines to an approved vaccine within class. However, challenges arose with the availability of comparator vaccines, making conducting these studies difficult.
    - Regulators subsequently agreed that study designs can be based on either non-inferiority immunogenicity if the comparator vaccine has demonstrated high efficacy and/or superiority if the comparator vaccine has demonstrated modest efficacy.
    - It may be preferable to compare against higher (rather than modest) efficacy vaccines to give the additional margin needed to be confident the vaccines work.
    - Over the next six to nine months, developers are likely to shift from a primary series to pursue a boosting strategy (where a candidate vaccine is added to an approved homologous series which has demonstrated vaccine efficacy).
    - In the event the neutralising antibody titre against the higher efficacy vaccine does not quite meet the primary criteria for approval/licensure, the totality of data (i.e., other primary series compared against, animal models, etc.) should be considered to provide confidence that the level of neutralising antibodies is significant enough to warrant a label claim.
    - Further data from heterologous primary series and heterologous boosting studies will enable a better understanding of the immune response and what is required for an efficacious vaccine. This would need to be demonstrated post licensure via effectiveness studies.

- *In addition to GMTs, can seroprotection or seroconversion rates be used in a non-inferiority study?*
    - Vaccines that induce very high immune responses should not be subjected to the same level of rigor as vaccines that give rise to lower immune responses, especially in a public health emergency.
    - The situation is more complex for vaccines that only give rise to a modest immune response and these additional variables might apply to such vaccines.

- *How important is a four-fold titre increase in a seropositive population?*
    - In protected individuals with already high antibody titres, an additional vaccine dose will not result in a four-fold increase. In addition, assays are not reliable at distinguishing an extremely high titre from a very high titre.
    - A more sophisticated approach is required in terms of how seroresponse rates are considered.

- *Rather than just single licensure criteria, should other immunogenicity readouts (e.g., cellular immune response) also be included although difficult to base non-inferiority assessments on?*
    - Developers should devise sophisticated designs that could generate an authorisation path and then approach the regulators to move forward.
    - It is important not to lose the 85-90% effective vaccines; however, we should not be struggling to put marginal vaccines on the market for any jurisdiction, particularly LMICs.
    - Products with more marginal efficacy at two doses should be exploring three or more doses to make them more effective and clinically useful.

Wrap up and next steps

Dr Jakob Cramer, CEPI, thanked attendees for their participation in the workshop.

Closing remarks included:

- The Workshop report will be distributed following the meeting.
- Resources will continue to be shared at: https://epi.tghn.org/covax-overview/clinical-science/
- The COVAX Clinical SWAT Team plans to continue sharing learnings across developers as we pursue our common goal – a global supply of safe and effective vaccines.
- WHO BP team and COVAX Clin Dev SWAT team to co-organise a workshop on 'fractional dosing' – date TBC.